

Article

C-C Coupling Reactions between Benzofurazan Derivatives and 1,3-Diaminobenzenes

Gabriele Micheletti ^{1,*}, Silvia Bordoni ¹, Elena Chugunova ² and Carla Boga ^{1,*}

¹ Department of Industrial Chemistry 'Toso Montanari', Alma Mater Studiorum Università di Bologna Viale Del Risorgimento, Bologna 4402136, Italy; Silvia.bordoni@unibo.it

² A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, Akad. Arbuzov st. 8, Kazan, Tatarstan 420088, Russia; chugunova.e.a@gmail.com

* Correspondence: gabriele.micheletti3@unibo.it (G.M.); carla.boga@unibo.it (C.B.); Tel.: +39-051-209-3616 (C.B.)

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Abstract: Aromatic substitution reactions between 1,3-diaminobenzene and chloronitrobenzofurazan derivatives have never been reported so far. The aim of the current study was to synthesize novel electron-donor and -acceptor architectures of interest in applied fields and to provide new insights on the nucleophilic behavior of 1,3-diaminobenzenes. The reaction of 1,3-dipiperidinyl-, 1,3-dimorpholinyl-, 1,3-dipyrrolidinyl-, or 1,3-dimethylamino-benzene with 7-chloro-4,6-dinitrobenzofuroxan or with a series of chloro-nitrobenzofurazans has been carried out in mild conditions. The partners reactivity has been investigated by monitoring the reaction course through ¹H-NMR spectroscopy. The reaction occurred in a regioselective way, providing in good yields the novel C-C coupling compounds. Indications on the reactivity behavior for the studied nucleophiles have been relieved.

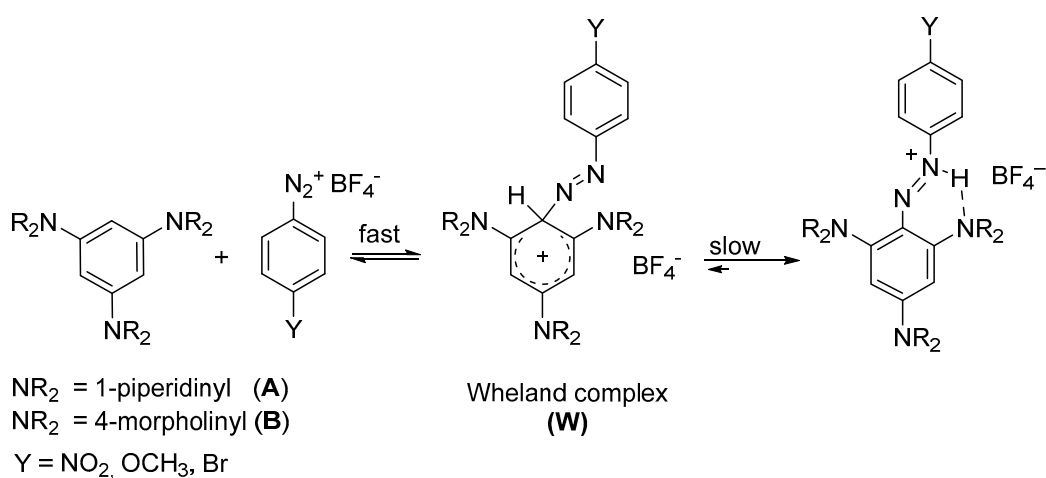
Keywords: benzofurazans; aromatic substitution; 1,3-diaminobenzenes

1. Introduction

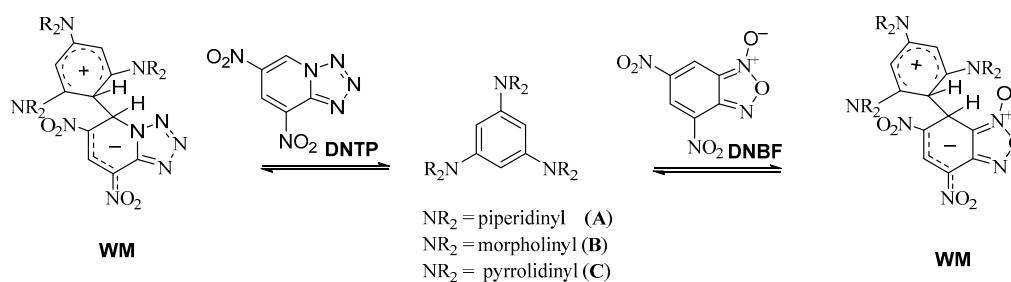
The aromatic substitution is one of the most exploited reactions in organic chemistry. The reaction can simply be indicated as aromatic substitution if both the reagents are aromatic, whereas the distinction into S_EAr and S_NAr has been invoked when only one reagent is aromatic. The case of C-C coupling between neutral aromatic substrates requires opposite features in the reagents (i.e., electron-rich vs. electron-poor). The 1,3,5-triaminobenzene derivatives—first studied by the pioneer work of Effenberger [1]—belong to neutral electron-rich aromatic substrates and are able to react at the neutral carbon atom [1,2]. (These kinds of nucleophiles have been reported to react with a plethora of electrophiles, such as proton [1–10], halogens [11,12], acyl- [13–15], alkyl- [16], and aryl-halides [17]. The coupling between 1,3,5-triaminobenzene of types **A** and **B** and aryl diazonium salts gave stable Wheland intermediates (**W**) by the azo-coupling reaction [18] (Scheme 1), conversely to what is usually reported in the textbooks. They provided evidence of the reversibility [19], and the proton departure from Wheland intermediate as the rate-determining step [20].

The coupling of 1,3,5-triaminobenzenes **A–C** (Scheme 2) with 4,6-dinitrobenzofuroxan (**DNBF**) provided the first example of characterized Wheland-Meisenheimer (**WM**) intermediate. The zwitterionic nature is generated by the contemporary presence of Wheland on the nucleophilic fragment and Meisenheimer on the electrophilic one. Further, **WM** intermediates have been identified by the sym-triaminobenzenes with 4,6-dinitrotetrazolopyridine (**DNTP**) or 2,3,4-trinitrothiophene [21]. 4,6-Dinitrobenzofuroxan (**DNBF**) and 4,6-dinitrotetrazolopyridine (**DNTP**) are 10π electron-deficient

heteroaromatics exhibiting reactivity behavior to be ranked as “superelectrophilic heteroaromatics” [22,23]. Their Mayr electrophilicity values [24–28] are -5.06 [29] and -4.67 , [22], respectively.



Scheme 1. Simplified reaction pathway of the azo coupling reaction.



Scheme 2. The first examples of detection and characterization of Wheland-Meisenheimer (WM) intermediates. DNBF: 4,6-dinitrobenzofuroxan; DNTP: 4,6-dinitrotetrazolopyridine.

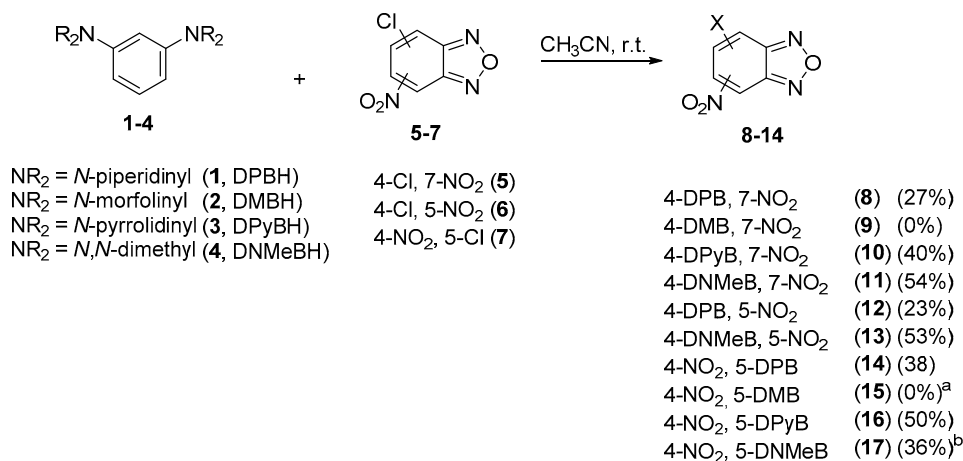
Finally, DNBF and DNTP gave WM intermediates by C-C coupling with other nucleophilic substrates, such as 2-aminothiazole [30] or 2,4-di(pyrrolidiny)thiazole [31]. Further, the C-C coupling between a series of chloro-nitrobenzofurazans and sym-triaminobenzenes gave access to highly conjugated structures of interest in the material field [32]. In the study, the first Wheland intermediate in benzofurazan series was isolated and fully characterized [32]. Among the mechanistic studies here described, it is noteworthy that benzofuroxans and benzofurazans are interesting reagents from a biological point of view—for example, as fluorescent probes [33,34] or fungicides [35]. Nitric oxide constitutes a biologically important molecule of the endothelium-derived relaxing factor, and the benzofuroxan moiety is well known for its ability to release NO under physiological conditions [36,37]. Several derivatives obtained from the combination of a benzofuroxanyl moiety with distinct bioactive substructure have recently received particular attention as anti-inflammatory [38] or antimicrobial agents [39]. Moreover, nitrobenzofurazans and nitrobenzofuroxans are also recognized to be versatile compounds in optoelectronic, agrochemical, or material fields [40,41].

Contrarily to the case of 1,3,5-triaminobenzenes, few examples of C-C coupling involving diaminobenzene derivatives [17,42–44] are present in the literature, likely due to their minor carbon nucleophilicity with respect to 1,3,5-triaminobenzenes.

Scarce literature reports on the reactivity of 1,3-diaminobenzenes suggested that we react them with 7-chloro-4,6-dinitrobenzofuroxan and chloro-nitrobenzofurazan derivatives. We investigated the reactivity of these nucleophiles to achieve compounds of interest for applications related to the simultaneous presence of electron-poor and electron-rich functions on the same scaffold.

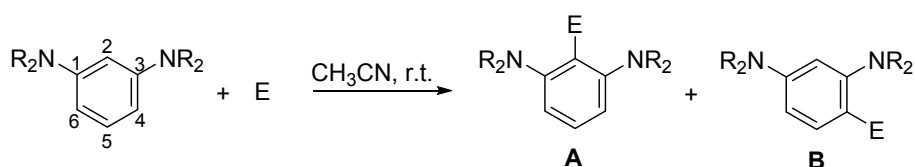
2. Results and Discussion

The reaction between 1,3-bis(*N,N*-dialkylamino)benzenes **1–4** (indicated thereafter by the acronyms shown in Scheme 3) and the chloro-nitrobenzofurazans **5–7** was carried out in acetonitrile at room temperature with an equimolar amount of reagents.



Scheme 3. Combination between nucleophiles **1–4** and electrophiles **5–7**. ^a Reaction run at 80 °C also with no conversion improving. ^b In the presence of alumina, the yield became 60%. DPBH: 1,3-bis(*N*-piperidinyl)benzene, DMBH: 1,3-bis(*N*-morpholinyl)benzene, DPyBH: 1,3-bis(*N*-pyrrolidinyl)benzene, DNMeBH: 1,3-bis(dimethylamino)benzene; DPB: 1,3-bis(*N*-piperidinyl)phenyl; DMB: 1,3-bis(*N*-morpholinyl)phenyl; DPyB: 1,3-bis(*N*-pyrrolidinyl)phenyl; DNMeB: 1,3-bis(dimethylamino)phenyl.

Two distinct isomers (**A** and **B** in Scheme 4) might be expected from the attack of the bis(dialkyl)aminobenzene (Scheme 4) at the carbon atom in position 2 or 4. As a matter of fact, the isomer **B** has solely been formed. By preventing the nucleophilic attack in position 2, steric hindrance did not likely permit the formation of isomer **A**.



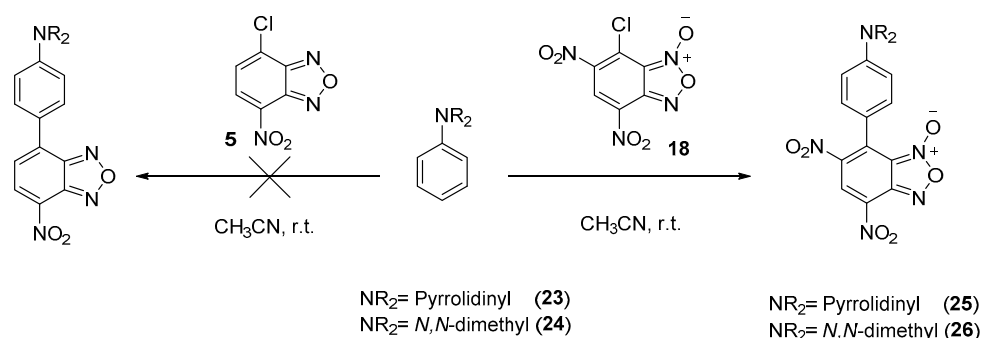
Scheme 4. Possible reaction products derived from the reaction of 1,3-diaminobenzene derivatives with electrophilic reagents.

The C-C coupling products were purified by flash chromatography (FC) on silica gel column and were fully characterized. In the cases of the reactions involving 1,3-bis(*N*-morpholinyl)benzene (DMBH, **2**), no product was formed, even by increasing the reaction temperature within 80 °C. Yields shown in Scheme 3 were calculated without considering that a half equivalent of the nucleophile might react with the hydrochloric acid formed as reaction co-product. This salification may be responsible for decreasing the nucleophilic efficiency so that a 50% row-yield was the maximum expected. Conversely, the achieved 54%/53% yields after work-up process for compounds **11/13**, respectively, suggests that protonation on the reaction products might occur, as previously observed in the case of triaminobenzenes with benzofurazans **5–7** [32]. Occasionally, to remove the formed HCl from the reaction mixture, some experiments were run in the presence of basic alumina. Neutralization procedure increased the yield in few cases, probably ascribed to the disrupting interactions with the Al₂O₃ stationary phase.

benzofurazan to benzofuroxan, the influence of the *N*-oxide in the pentatomic heteroaromatic ring was almost negligible [45,46].

By comparing the reaction data between **5** and the nucleophiles **1**, **3**, and **4** after 10 min (time within the salification process of the starting nucleophile and/or the reaction product can be considered negligible), the conversion relative on the nucleophilic species is DPBH < DNMeBH < DPyBH. Since the nucleophilicity of compounds **1–4** have not been reported so far, the above trend can be correlated to the nucleophilicity values of the substituent, in agreement with the equation developed by Mayr: $N_{\text{Mayr}} = 15.65, 17.35, \text{ and } 18.64$ for morpholine, piperidine, and pyrrolidine [47], and 17.96 for dimethylamine [48], respectively. Similar considerations can be made by analyzing the reactions of **1** and **3** with **7** (entries 6, 8) and reactions of **1**, **2**, and **3** with **18** (entries 9, 10, 12). The reaction conversions of **7**, **18** with substrate **4** resulted lower or comparable with respect to the reaction with **1** or **2**; this observation might be explained by considering two distinct factors: steric hindrance due to both the proximity (*ortho*-position) of the nitro groups in the electrophile, and that of the dimethylamino group on the incoming nucleophile.

To confirm this hypothesis and also to extend the study to the reactivity of monoaminobenzene derivatives, we reacted the chloro-nitrobenzofurazan **5** and the chlorodinitrobenzofuroxan **18** with *N*-pyrrolidinylbenzene (**23**) and *N,N*-dimethylaminobenzene (**24**) (Scheme 6) in equimolar amounts, and monitored the reaction course via by $^1\text{H-NMR}$ spectroscopy.

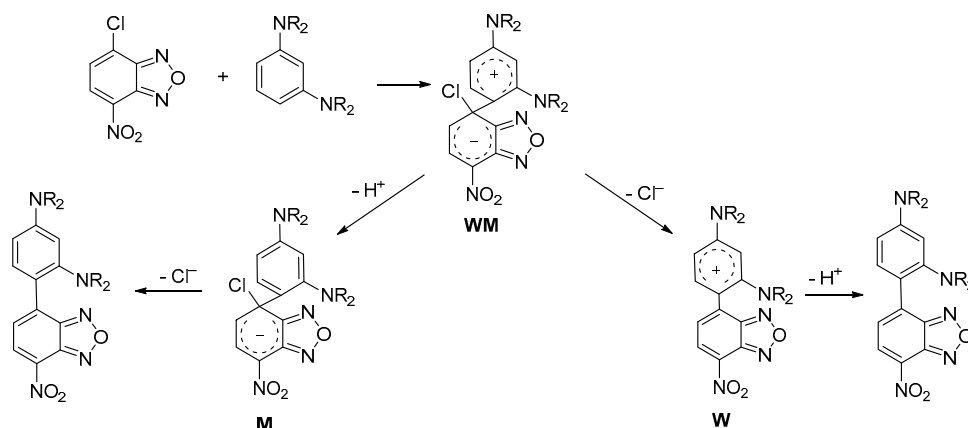


Scheme 6. Reaction between **5** and **18** and monoaminobenzenes **23–24**.

We found that **5** did not react with either **23** or **24**, whereas the reactions with **18** occurred at room temperature to afford the C-C coupling in *para*-position with respect to the amino group of the nucleophile. Specifically, the $^1\text{H-NMR}$ spectrum showed a 44% and 23% conversion, respectively, for **23** and **24** after 10 min. These findings are in agreement with the nucleophilicity values of the amino substituent reported above, and support the occurrence of steric hindrance to explain the unexpected very low conversion to **22** (Table 1, entry 11). The absence of the crowding in monoaminobenzenes permitted the formation of products **25** (from **18** and **23**) and **26** (from **18** and **24**), and thus gave a further confirmation of the increase in the reactivity of the electrophile ascribed to the presence of an additional nitro group.

Finally, the proposed mechanism for the current $\text{S}_{\text{E}}\text{Ar}/\text{S}_{\text{N}}\text{Ar}$ reactions (shown in Scheme 7 for compound **5**) implies the formation of **WM** zwitterionic intermediate. The intermediate might evolve into a cationic Wheland-like intermediate (**W**) through the chloride displacement or to an anionic Meisenheimer like (**M**) intermediate via proton expulsion. The final substitution product can be generated from both intermediates. Due to presence of a chloride leaving group, the σ -anionic intermediate **M** (as well as **WM**) is an elusive species, which to the best of our knowledge has never been detected. The presence of electron-donor groups on the nucleophilic fragment might be responsible for the stabilization of **W** intermediate to let it be detectable. In the case of reaction between **5** and 1,3,5-tris(pyrrolidinyl)benzene [32], we already reported the isolation and characterization of **W**-type intermediate. The efforts to analogously trap elusive species in the NMR

tube at low temperature for the reactions reported in Scheme 7 did not afford analogous results, indicating that the electronic features of two amino groups are not sufficient requisites to stabilize the σ -cationic intermediate.



Scheme 7. Possible intermediates in the S_EAr/S_NAr reaction between chloro-nitrobenzofurazans and 1,3-diaminobenzene derivatives.

3. Materials and Methods

3.1. General Methods

The 1H spectra were recorded with a Mercury 400 (Varian, Palo Alto, CA, USA) spectrometer operating at 400 MHz for 1H -NMR and 100.56 MHz for ^{13}C -NMR. Signal multiplicities were established by Distortioless Enhanced by Polarization Transfer (DEPT) experiments. Chemical shifts were measured in δ (ppm) with reference to the solvent ($\delta = 7.26$ ppm and 77.00 ppm for $CDCl_3$, for 1H -, and ^{13}C -NMR, respectively). J values are given in Hz. Electron spray ionization mass spectra (ESI-MS) were recorded with a WATERS 2Q 4000 instrument (Waters Corporation, Milford, MA, USA). IR spectra were recorded on a Perkin Elmer FT-IR spectrometer (Perkin Elmer, Waltham, MA, USA) Spectrum Two equipped with a UATR TWO ATR accessory (diamond crystal, DTGS detector; spectral resolution 4 cm^{-1}). Chromatographic purifications (FC) were carried out on glass columns packed with silica gel (Merck grade 9385, 230–400 mesh particle size, 60 \AA pore size) at medium pressure. Thin layer chromatography (TLC) was performed on silica gel 60 F254 coated aluminum foils (Fluka Chemie GmbH, Buchs, Switzerland).

3.2. Synthesis of 1,3-Di(piperidin-1-yl)benzene (1) and N^1,N^1,N^3,N^3 -Tetramethylbenzene-1,3-diamine (4)

To a solution of 1,3-dichlorobenzene (0.85 mL, 7.45×10^{-3} mol) and amine (piperidine or dimethylamine 0.06 mol) in 50 mL of anhydrous THF, under nitrogen atmosphere, phenyl lithium (30 mL, 0.06 mol) was added dropwise. The mixture was stirred for 24 h at room temperature, then was quenched with water (50 mL). The organic layer was separated, and the aqueous fraction was extracted with diethyl ether (3×30 mL). The organic layer was anhydridified over magnesium sulfate and filtered. The product was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 2:1). The chemico-physical data of 1 [49,50] and 4 [51] are in good agreement with those reported in the literature.

3.3. Synthesis of 1,3-Dimorpholinobenzene (2) and 1,3-Di(pyrrolidin-1-yl)benzene (3)

The reaction was carried out in autoclave. Amine (morpholine or pyrrolidine, 0.07 mol) and potassium *tert*-butylate (5.4 g, 0.048 mol) were added to the solution of 1,3-dichlorobenzene (1.37 mL, 0.011 mol) in toluene (10 mL). The reaction was left at $160\text{ }^\circ\text{C}$ for 4 days under magnetic stirring, then it was allowed to stand at room temperature and quenched with water (50 mL). The organic

layer was separated, and the aqueous fraction was extracted with dichloromethane (3 × 30 mL). The organic layer was dried over anhydrous magnesium sulfate. The product was purified by column chromatography on silica gel. The chemico-physical data of **2** [49,50] and **3** [52] are in good agreement with those reported in the literature.

3.4. Reactions between (*N,N*-Dialkyl)-diaminobenzenes (**1–4**) and Compounds **5–7**—General Procedure

To a stirred solution of (*N,N*-dialkyl)-diaminobenzene (0.1 mmol) in acetonitrile (5 mL), an equimolar amount of electrophile was added. The reaction was left at room temperature under magnetic stirring for about 12 h. The product was purified by column chromatography on silica gel. An analogous procedure but with a 2/1 nucleophile/electrophile relative molar ratio was used for the reactions of **18** with **5–7**, **23**, **24**; reactions of **5** with **23** and **24** did not work.

4-(2,4-Di(piperidin-1-yl)phenyl)-7-nitrobenzo[c][1,2,5]oxadiazole (8): eluent: *n*-hexane/ethyl acetate 8/2; yield 27%; brown solid, m.p.: >200 °C (dec); IR (ν , cm^{-1}): 1601, 1503, 1299, 1235; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.52 (d, $J = 8.1$ Hz, 1H); 8.26 (br.s, 1H); 7.66 (d, $J = 8.1$ Hz, 1H); 6.64 (br.s, 2H); 3.35 (br.s, 4H); 2.85 (br.s, 4H); 1.85–1.60 (m, 6H); 1.46 (br.s, 6H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 154.5; 154.0; 150.1; 143.5; 139.5; 133.7; 131.3; 125.8; 116.8; 109.0; 105.8; 53.4; 49.1; 25.9; 25.5; 23.9; ESI-MS (m/z): 408 $[\text{M} + \text{H}]^+$, 430 $[\text{M} + \text{Na}]^+$, 446 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{26}\text{N}_5\text{O}_3$ 408.2036 found 408.2038.

4-(2,4-Di(pyrrolidin-1-yl)phenyl)-7-nitrobenzo[c][1,2,5]oxadiazole (10): eluent: petroleum light/diethyl ether 1/1; yield 40%; brown solid, m.p.: >280 °C (dec); IR (ν , cm^{-1}): 1605, 1499, 1288, 1235; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.49 (d, $J = 8.2$ Hz, 1H); 7.72 (d, $J = 8.9$ Hz, 1H); 7.25 (d, $J = 8.3$ Hz, 1H); 6.27 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.2$ Hz, 1H); 6.10 (s, 1H), 3.41 (t, $J = 6.7$ Hz, 4H), 3.06 (t, $J = 6.7$ Hz, 4H); 2.10–2.03 (m, 4H); 1.89–1.81 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 150.4; 150.1; 149.9; 143.6; 140.5; 134.7; 132.0; 130.9; 124.1; 111.3; 104.7; 97.3; 52.2; 48.0; 25.7; 25.4; ESI-MS (m/z): 380 $[\text{M} + \text{H}]^+$, 402 $[\text{M} + \text{Na}]^+$, 418 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{N}_5\text{O}_3$ 380.1723 found 380.1724.

N^1, N^1, N^3, N^3 -Tetramethyl-4-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)benzene-1,3diamine (11): eluent: petroleum light/diethyl ether 4/6; yield 54%; brown solid, m.p.: >280 °C (dec); IR (ν , cm^{-1}): 1600, 1478, 1297, 1235; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.51 (d, $J = 8.0$ Hz, 1H); 8.01 (d, $J = 7.6$ Hz, 1H); 7.73 (d, $J = 8.6$ Hz, 1H); 6.49 (d, $J = 8.6$ Hz, 1H); 6.43 (s, 1H); 3.09 (s, 6H); 2.68 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 153.6; 152.2; 150.1; 143.7; 139.6; 134.4; 132.5; 131.8; 125.2; 114.9; 106.6; 102.6; 43.9; 40.7; ESI-MS (m/z): 328 $[\text{M} + \text{H}]^+$, 350 $[\text{M} + \text{Na}]^+$, 366 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{18}\text{N}_5\text{O}_3$ 328.1410 found 328.1413.

4-(2,4-Di(piperidin-1-yl)phenyl)-5-nitrobenzo[c][1,2,5]oxadiazole (12): eluent: petroleum light/diethyl ether 9/1; yield 23%; dark blue solid, m.p.: >80 °C (dec.); IR (ν , cm^{-1}): 1598, 1502, 1285, 1234; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 7.91 (d, $J = 9.5$ Hz, 1H); 7.82 (d, $J = 9.5$ Hz, 1H); 7.42 (d, $J = 8.4$ Hz, 1H); 6.85–6.54 (m, 2H); 3.31 (br.s, 4H); 2.70–2.53 (m, 4H); 1.9–1.59 (m, 8H); 1.35 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 153.9; 150.7; 149.2; 146.3; 131.7; 128.0; 126.7; 114.5; 109.7; 107.4; 53.6; 49.4; 25.8; 25.5; 24.8; ESI-MS (m/z): 408 $[\text{M} + \text{H}]^+$, 430 $[\text{M} + \text{Na}]^+$, 446 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{26}\text{N}_5\text{O}_3$ 408.2036 found 408.2037.

N^1, N^1, N^3, N^3 -Tetramethyl-4-(5-nitrobenzo[c][1,2,5]oxadiazol-4-yl)benzene-1,3diamine (13): eluent: ethyl acetate/dichloromethane 8/2; yield 53%; brown solid, m.p.: >155 °C (dec); IR (ν , cm^{-1}): 1602, 1490, 1289, 1236; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 7.81 (d, $J = 9.4$ Hz, 1H); 7.77 (d, $J = 9.4$ Hz, 1H); 7.46 (d, $J = 9.0$ Hz, 1H); 6.52 (d, $J = 9.0$ Hz, 1H); 6.41 (br.s, 1H); 3.06 (s, 6H); 2.45 (br.s, 6H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 153.4; 152.5; 150.6; 149.2; 145.9; 132.1; 128.2; 126.4; 113.9; 112.3; 106.5; 103.1; 42.0; 40.3; ESI-MS (m/z): 328 $[\text{M} + \text{H}]^+$, 350 $[\text{M} + \text{Na}]^+$, 366 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{18}\text{N}_5\text{O}_3$ 328.1410 found 328.1411.

5-(2,4-Di(piperidin-1-yl)phenyl)-4-nitrobenzo[c][1,2,5]oxadiazole (**14**): eluent: ethyl acetate/dichloromethane 2/8; 38%; brown solid, m.p.: >120 °C (dec); IR (ν , cm^{-1}): 1598, 1506, 1319, 1235; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 7.96 (d, $J = 9.0$ Hz, 1H); 7.67 (d, $J = 9.0$ Hz, 1H); 7.10 (br.s, 1H); 6.63 (br.s, 2H); 3.30 (br.s, 4H); 2.84 (br.s, 4H); 1.73 (br.s, 4H); 1.64 (br.s, 4H); 1.43 (br.s, 4H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 154.2; 153.5; 149.0; 144.2; 140.9; 137.2; 130.8; 122.5; 121.3; 118.7; 110.0; 106.1; 53.5; 49.3; 29.7; 25.9 (two signals overlapped); 24.1; ESI-MS (m/z): 408 $[\text{M} + \text{H}]^+$, 430 $[\text{M} + \text{Na}]^+$, 446 $[\text{M} + \text{K}]^+$ HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{26}\text{N}_5\text{O}_3$ 408.2036 found 408.2033.

5-(2,4-Di(pyrrolidin-1-yl)phenyl)-4-nitrobenzo[c][1,2,5]oxadiazole (**16**): eluent: ethyl ether/petroleum light 7/3; yield 50%; orange solid, m.p.: >115 °C (dec); IR (ν , cm^{-1}): 1601, 1503, 1321, 1233; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 7.89 (d, $J = 9.4$ Hz, 1H); 7.62 (d, $J = 9.4$ Hz, 1H); 7.05 (d, $J = 8.6$ Hz, 1H); 6.34–6.25 (m; 2 H, two signals overlapped); 3.42 (t, $J = 6.5$ Hz, 4H), 3.16 (s; 2H); 3.04 (s, 2H) 2.08 (t, $J = 6.48$ Hz, 4H); 1.83 (t, $J = 6.33$ Hz, 4H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 149.4; 148.9; 144.3; 142.2; 136.5; 132.1; 118.9; 105.8; 100.8; 51.7; 50.0; 25.6; 25.2; (selected data); ESI-MS (m/z): 380 $[\text{M} + \text{H}]^+$, 402 $[\text{M} + \text{Na}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{N}_5\text{O}_3$ 380.1723 found 380.1723.

$\text{N}^1, \text{N}^1, \text{N}^3, \text{N}^3$ -Tetramethyl-4-(4-nitrobenzo[c][1,2,5]oxadiazol-5-yl)benzene-1,3diamine (**17**): eluent: ethyl ether/petroleum light 3/7; yield 36%; brown solid, m.p.: >130 °C (dec); IR (ν , cm^{-1}): 1604, 1498, 1315, 1237; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 7.94 (d, $J = 9.4$ Hz, 1H); 7.64 (d, $J = 9.4$ Hz, 1H), 7.11 (d, $J = 8.6$ Hz, 1H); 6.50 (br.s, 2H, two signals overlapped); 3.07 (s, 6H), 2.65 (s, 6H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 152.9; 152.1; 149.0; 148.9; 144.3; 140.8; 136.4; 132.8; 131.4; 127.5; 119.1; 107.7; 103.5; 43.3; 41.2; ESI-MS (m/z): 328 $[\text{M} + \text{H}]^+$, 350 $[\text{M} + \text{Na}]^+$, 366 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{18}\text{N}_5\text{O}_3$ 328.1410 found 328.1413.

7-(2,4-Di(piperidin-1-yl)phenyl)-4,6-nitrobenzo[c][1,2,5]oxadiazole-1-oxide (**19**): eluent: ethyl ether/petroleum light 1/1; yield 80%; brown solid, m.p.: >280 °C (dec); IR (ν , cm^{-1}): 1610, 1554, 1520, 1312; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.80 (s, 1H); 7.66 (d, $J = 9.7$ Hz, 2 H, two signals overlapped); 6.66 (br.s, 1H); 3.43–3.30 (m, 4H); 2.91–2.75 (m, 4H); 1.77 (br.s, 2H); 1.69 (s, 2H); 1.49 (br.s, 4H); ESI-MS (m/z): 469 $[\text{M} + \text{H}]^+$, 491 $[\text{M} + \text{Na}]^+$, 507 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{25}\text{N}_6\text{O}_6$ 469.1836 found 469.1838.

7-(2,4-Di(morpholin-1-yl)phenyl)-4,6-nitrobenzo[c][1,2,5]oxadiazole-1-oxide (**20**): eluent: ethyl acetate/*n*-hexane 7/3; yield 80%; brown solid, m.p.: >280 °C (dec); IR (ν , cm^{-1}): 1607, 1549, 1515, 1313; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.77 (s, 1H); 7.00 (d, $J = 9.0$ Hz, 1H); 6.67 (dd, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, 1H); 6.62 (d, $J = 1.85$ Hz, 1H); 3.87 (t, $J = 4.6$ Hz, 4H); 3.50–3.39 (m, 4H); 3.35 (t, $J = 4.6$ Hz, 4H); 2.97–2.78 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 154.3; 153.9; 144.3; 142.1; 134.1; 133.9; 131.1; 127.7; 113.7; 111.8; 110.3; 105.5; 67.0; 66.3; 52.8; 47.8. ESI-MS (m/z): 473 $[\text{M} + \text{H}]^+$, 495 $[\text{M} + \text{Na}]^+$, 511 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{21}\text{N}_6\text{O}_8$ 473.1421 found 473.1423.

7-(2,4-Di(pyrrolidin-1-yl)phenyl)-4,6-nitrobenzo[c][1,2,5]oxadiazole-1-oxide (**21**): eluent: ethyl ether/petroleum light 1/1; yield 65%; brown solid, m.p.: >250 °C (dec); IR (ν , cm^{-1}): 1609, 1546, 1516, 1313; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.85 (s, 1H); 7.01 (d, $J = 8.7$ Hz, 1H); 6.75 (d, $J = 8.7$ Hz, 1H); 6.72 (br.s, 1H); 3.68–3.59 (m, 4H); 4.48–3.41 (m, 4H); 2.17–2.05 (m, 8H); ESI-MS (m/z): 441 $[\text{M} + \text{H}]^+$, 463 $[\text{M} + \text{Na}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{21}\text{N}_6\text{O}_6$ 441.1523 found 441.1526.

7-(2,4-Bis(dimethylamino)phenyl)-4,6-nitrobenzo[c][1,2,5]oxadiazole-1-oxide (**22**): eluent: ethyl ether/petroleum light 8/2; yield 65% (70% in presence of Al_2O_3); brown solid, m.p.: >130 °C (dec); IR (ν , cm^{-1}): 1612, 1545, 1510, 1314; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.88 (s, 1H); 7.66 (d, $J = 8.9$ Hz, 1H); 6.56 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.1$ Hz, 1H); 6.35 (s, 1H); 3.14 (s, 6H), 2.54 (s, 6H); $^{13}\text{C-NMR}$ (CDCl_3 : 100.56 MHz, 25 °C): δ (ppm): 154.1; 151.8; 143.2; 142.3; 134.2; 133.5; 131.4; 128.2; 111.3; 107.2; 102.4; 43.2; 40.2; ESI-MS (m/z): 389 $[\text{M} + \text{H}]^+$, 411 $[\text{M} + \text{Na}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{17}\text{N}_6\text{O}_6$ 389.1210 found 389.1211.

4,6-Dinitro-7-(4-(pyrrolidin-1-yl)phenyl)benzo[*c*][1,2,5]oxadiazole 1-oxide (**25**): eluent: petroleum light/diethyl ether 6/4; yield 66%, dark blue solid; m.p. > 280 °C (dec); IR (ν , cm^{-1}): 1614, 1556, 1522, 1312; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.68 (s, 1H), 7.23 (d, $J = 8.71$ Hz, 2H), 6.63 (d, $J = 8.71$ Hz, 2H), 3.43 (t, $J = 6.37$ Hz, 4H), 2.08 (t, $J = 6.37$ Hz, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 100.56 MHz) δ (ppm): 150.4, 147.7, 141.4, 134.6, 131.5 (CH), 127.9 (CH), 113.5, 112.3, 111.8 (CH), 110.9, 47.7 (CH_2), 25.4 (CH_2); ESI-MS (m/z): 372 $[\text{M} + \text{H}]^+$, 394 $[\text{M} + \text{Na}]^+$; HRMS (ES^+) m/z : ($\text{M} + \text{H}$) $^+$ calculated for $\text{C}_{16}\text{H}_{14}\text{N}_5\text{O}_6$ 372.0944 found 372.0946.

7-(4-(Dimethylamino)phenyl)-4,6-dinitrobenzo[*c*][1,2,5]oxadiazole 1-oxide (**26**): petroleum light/diethyl ether 4/6; yield 62% dark blue solid; m.p.: >145 °C (dec); IR (ν , cm^{-1}): 1610, 1554, 1521, 1309; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz, 25 °C): δ (ppm): 8.69 (s, 1H), 7.24 (d, $J = 9.10$ Hz, 2H), 6.76 (d, $J = 9.10$ Hz, 2H), 3.12 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 100.56 MHz) (selected data) δ (ppm): 152.7, 144.6, 131.2 (CH), 127.8 (CH), 111.5 (CH), 40.0 (CH_3); ESI-MS (m/z): 346 $[\text{M} + \text{H}]^+$, 368 $[\text{M} + \text{Na}]^+$, 384 $[\text{M} + \text{K}]^+$; HRMS (ES^+) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{12}\text{N}_5\text{O}_6$ 346.0788 found 346.0790.

4. Conclusions

The nucleophile/electrophile combinations between 1,3-dialkylaminobenzene derivatives **1–4** and the chloro-nitrobenzofurazan derivatives **5–7** or the chloro-dinitrobenzofuroxan **18** occurred regioselectively, yielding the product from the attack in the less-hindered *ortho*-position to the amino groups located on the aromatic ring of the nucleophile. The novel synthesized compounds are highly conjugated systems contemporarily bearing an electron-rich and an electron-poor moiety. This characteristic feature makes them interesting candidates for eventual future applications in applied fields, such as solar cells, optoelectronic, and chromogenic materials. In the case of benzofuroxan derivatives, in the pharmaceutical field as NO release agents.

Further, the extension to some monoaminobenzene derivatives as nucleophiles permits to highlight the effect of steric encumbrance of the amino substituents on the reactivity of the considered systems on going from mono- to towards polysubstituted species.

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Author Contributions: C.B. conceived, designed the experiments and analyzed the data; G.M. and E.C. performed the experiments and analyzed the data; C.B. and S.B. wrote the paper.

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